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Inherited epithelial transporter disorders—an overview

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Summary In the late 1990s, the identification of transporters and transporter-associated genes progressed substantially due to the development of new cloning approaches such as expression cloning and, subsequently, to the implementation of the human genome project. Since then, the role of many transporter genes in human diseases has been elucidated. In this overview, we focus on inherited disorders of epithelial transporters. In particular, we review genetic defects of the genes encoding glucose transporters (SLC2 and SLC5 families) and amino acid transporters (SLC1, SLC3, SLC6 and SLC7 families).

Abbreviations

ABC	ATP-binding cassette
ATS	arterial tortuosity syndrome
CAT	cationic amino acid transporter
EAAT	excitatory amino acid transporter
GGM	glucose/galactose malabsorption
GLUT	glucose transporter
gpaAT	glucoprotein-associated amino acid transporter
HAT	heterodimeric amino acid transporter
HGNC	HUGO Gene Nomenclature Committee
H^+ V-ATPase	vacuolar proton ATPase
IEM	inborn error of metabolism
LPI	lysinuric protein intolerance
NIS	sodium/iodide symporter
PT	proximal tubule
rBAT	related to $b^{0,+}$ amino acid transporter
RG	renal glucosuria
SGLT	sodium/glucose transporter
SLC	solute carrier
SIT1	sodium imino acid transporter 1
SNP	single nucleotide polymorphism
TM	transmembrane
y^+LAT1	y^+L-type amino acid transporter 1

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Introduction

The human genome contains approximately 2000 genes encoding membrane transporters and transporter-associated proteins (Landowski et al 2005). Transporters are integral proteins that play crucial physiological roles by participation, for example, in cellular nutrition and by regulating ionic, osmotic and acid–base homeostasis. They accomplish these important tasks by promoting the cellular or organellar uptake or efflux of vital substances such as sugars, amino acids, nucleotides, Krebs cycle intermediates, vitamins, organic and inorganic ions, urea, metals, water and drugs.

Transporters can be divided into three classes: channels, ATP-dependent transporters and solute carrier (SLC) proteins. (1) Channels are pore-forming structures that allow the passive translocation of ions,

water or other solutes along their electrochemical gradients across membranes. Ion channels often include 'gates' that can be opened or closed through diverse gating mechanisms. (2) In higher organisms, ATP-driven transporters allow the active cellular exit of solutes. Because these transporters use ATP hydrolysis as a primary energy source to drive active transport, they are termed primary-active transporters or pumps. ATP-binding cassette (ABC) transporters (such as the MDR multidrug resistance transporters) are ATP-dependent transporters that mediate the cellular exit of solutes. (3) The SLC families include the classical carrier proteins that transport solutes in a passive or secondary active mode (Hediger et al 2004). These transporters undergo sequential conformational changes during the transport cycle. SLC proteins include facilitated transporters that mediate the diffusion of solutes such as glucose, amino acids and urea across membranes down their electrochemical gradients (Fig. 1). SLC proteins can also transport more than one substrate simultaneously, with fixed coupling stoichiometries. Coupling of the transport of solutes to the cotransport of Na^+ or H^+ allows uphill solute transport against an electrochemical gradient (see Fig. 1). Such transporters are called secondary-active transporters. Examples are the intestinal Na^+/glucose cotransporter (SLC5A1) or the intestinal H^+-oligopeptide transporter (SLC15A1). In general, secondary-active transporters use the electrochemical gradients of ions generated by pumps (especially the ubiquitous Na^+,K^+-ATPase or the H^+ V-ATPase) to maintain the cellular homeostasis. The SLC proteins also encode a variety of antiporters or exchangers (transporters of substrates in opposite directions) and multiporters (transporters of substrates in both directions, Fig. 1).

The 'HUGO Gene Nomenclature Committee' (HGNC; http://www.genenames.org/) database includes over 45 SLC superfamilies which include a total number of almost 400 transporter genes. A website has been established (http://www.bioparadigms.org/SLC/menu.asp) that gives the latest updates on the SLC superfamilies and members, including their roles in human diseases. In general, these genes are numbered numerically using the root abbreviation SLC (e.g., SLC1, solute carrier family 1), followed by the letter 'A' (used solely as a spacer) and the number of the individual transporter (e.g., SLC1A2 for solute carrier family 1 member 2). A transporter is assigned to a specific family if it shows at least 15–25% amino acid sequence identity with the other members of that family. Although most of the SLC proteins are now cloned and functionally well characterized, a number of them are still 'orphans' because their transport function remains unknown.

SLC proteins are expressed in the plasma membranes or in membranes of intracellular compartments such as vesicles, lysosomes and mitochondria. Numerous inherited or acquired human diseases are caused by SLC protein dysfunction. To this end, the Online Mendelian Inheritance in Man (OMIM) web site (http://www.ncbi.nlm.nih.gov/sites/entrez/) lists all of the human inherited disease found to date and their related gene mutations SLC-related inborn errors of metabolism (IEMs) can be caused by mutations in the transporter genes themselves or in genes encoding regulatory components of the transporters such as enzymes or cytoskeleton proteins (Gamba 2005; Ikeda et al 2006).

There are several molecular mechanisms by which mutations can alter transporter activities with subsequent pathological consequences. Mutations can alter the membrane expression of transporters through changes in protein synthesis or protein processing,

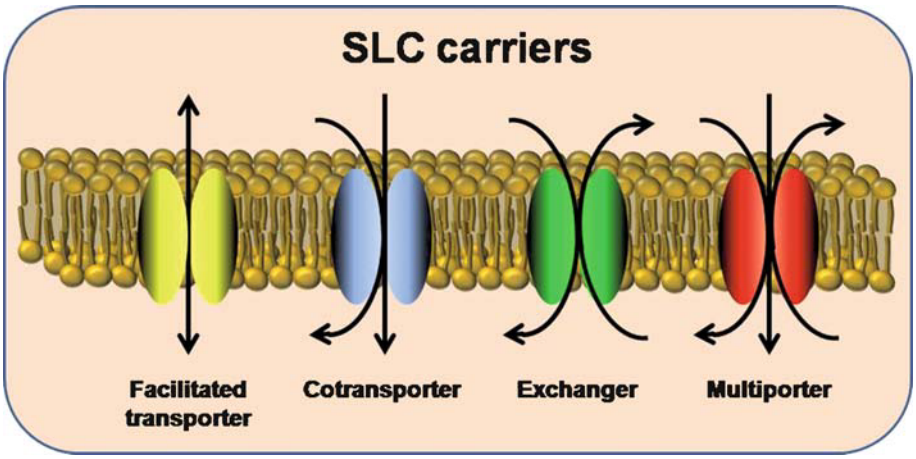

Fig. 1 Transport types of the SLC carriers

through altered membrane targeting or membrane insertion, or through direct changes in the functional properties of the protein. SLC proteins may also be involved in polygenic or acquired diseases such as epilepsy, osteoporosis, nephrolithiasis, diabetes, cancer and hypertension, for which the precise mechanism of pathogenesis is still unclear. Genetic approaches such as the identification of single nucleotide polymorphisms (SNPs), genotyping and transgenic strategies have been helpful in revealing the involvement of SLC proteins in human physiology and in elucidating their roles in human diseases. Clinical, molecular and functional studies are still required to confirm many of these findings.

Glucose transport

Glucose is essential for cellular metabolism and energy production. Transporters of glucose and related sugars are encoded by two SLC gene families: the SLC2 family of facilitated glucose transporters (also called GLUTs), and the SLC5 family of Na^+-coupled glucose cotransporters (also called SGLTs). Owing to their importance in human physiology, it is not surprising that each of these SLC families is associated with human diseases.

Inborn errors of the *SLC2* gene family

The SLC2 family contains 14 members: 12 facilitated glucose transporters (SLC2A1–12 or GLUT1–12), one fructose transporter (SLC2A5 or GLUT5) and one *myo*-inositol transporter (SLC2A13 or GLUT13). All *SLC2* genes encode transporters possessing 12 membrane-spanning domains, with N- and C-termini being localized intracellularly. Tissue- and cell-specific expression of the GLUT homologues underlies their specific role in the control of whole-body glucose homeostasis, which is supported by studies with transgenic mice (Heilig et al 2003). Inherited diseases are particularly linked to mutations encoding the GLUT1, GLUT2, GLUT4 and GLUT10 transporters.

In 1985, GLUT1 was the first transporter of this family to be cloned (Mueckler et al 1985). This protein is a high-affinity glucose transporter distributed in almost every tissue, although expression levels vary within different cell types. For example, GLUT1 is highly expressed in endothelial cells at the blood–brain barrier, where it constitutes an important glucose entry pathway into the brain (Agus et al 1997). The first defect in an SLC2 transporter was demonstrated by DeVivo et al (1991), who reported two SLC2A1-deficient patients with infantile seizures, delayed development and acquired microcephaly. These symptoms are consistent with a defect in glucose transport across the blood–brain barrier (OMIM 606777 in Table 1). In 2000, the designation 'GLUT1 deficiency syndrome' was used for the same disorder observed in 15 children in which heterozygous mutations in the *SLC2A1/GLUT1* gene were found (Wang et al 2000). This transport disorder has an autosomal dominant transmission mode. To date, several mutations in the *SLC2A1* gene were found to cause defects in glucose transport across the blood-brain barrier. Deletions, insertions, missense or nonsense mutations were identified in affected patients (Brockmann et al 2001; DeVivo et al 1991; Klepper et al 2001; Seidner et al 1998; Wang et al 2000). One of them, the p.Gly91Asp substitution, has been further studied functionally (Klepper et al 2001). This amino acid exchange affects a highly conserved cytoplasmic anchor point, the so-called R-X-G-R-R motif between helices 2 and 3. The GLUT1 protein expression at the plasma membrane was unchanged by this mutation, but was functionally impaired.

The *SLC2A2* gene encodes the facilitated glucose transporter GLUT2. It was isolated from adult human liver and kidney cDNA libraries and was found to have 55.5% identity with GLUT1. The encoded protein is particularly distributed in intestine, kidney, liver and pancreas: tissues known to have high-capacity glucose transport systems (Fukumoto et al 1988). GLUT2 is present in the basolateral membrane of absorptive epithelial cells where it participates in the transepithelial transport of glucose, together with the apical Na^+-glucose cotransporters SLC5A1 or SLC5A2 (described below). In hepatocytes, GLUT2 is localized in the sinusoidal membrane where it controls the cellular uptake and efflux of glucose into the circulation. In the insulin-producing β-cells of the pancreas, GLUT2 resides in specific plasma membrane domains (Orci et al 1989). Functionally, GLUT2 facilitates the transport of glucose, galactose, mannose and fructose with low affinity and high capacity.

The defect of this protein is linked to several human diseases. The first mutation found in the *SLC2A2* gene was an amino acid substitution (p.Val197Ile), present in the heterozygous state in a patient with non-insulin-dependent diabetes mellitus (Mueckler et al 1994; Tanizawa et al 1994). Functional characterization of this mutation in *Xenopus* oocytes showed abolition of GLUT2 transport activity. However, it is still unclear whether the heterozygosity for this mutation is of clinical relevance or was just an incidental finding in this individual. The other known human disease

Table 1 Inborn errors of glucose metabolism caused by faulty cell surface SLCs

SLC member, DTT: substrates	OMIM no.	Disease name	Clinical, molecular and biological features	IM	Locus
SLC2A1, F: glucose	606777	Blood–brain barrier glucose transport defect	Infantile seizure, delayed development, acquired microcephaly, hypoglycorrhachia	D	1p35-p31.3
SLC2A2, F: glucose	227810	Fanconi–Bickel syndrome	Fever, vomiting, growth failure, and rickets, dwarfism, protuberant abdomen, hepatomegaly, moon-shaped face, and fat deposition about the shoulders and abdomen Later in life: rickets and osteoporosis, glucosuria, polyuria, glucose and galactose intolerance, hepatic and renal glycogen storage	R	3q26.1-q26.3
SLC2A10, F: glucose	208050	Arterial tortuosity syndrome	Tortuosity and elongation of all major arteries; micrognathia, elongated face, down-slanting palpebral fissures, blepharophimosis, and a beaked nose	R	20q12-q13.1
SLC5A1, C: Na^+/glucose	606824	Glucose/galactose malabsorption	Severe diarrhoea and dehydration, reduced capacity for glucose transport, absence of intestinal glucose transport, partial impairment of renal glucose transport	R	22q13.1
SLC5A2, C: Na^+/glucose	233100	Renal glucosuria	Low renal threshold for glucose, variable glucose excretion with the urine	R/D	16p11.2
SLC5A5, C: Na^+/iodide	274400	Genetic defect in thyroid hormogenesis	Mild goitre, multiple mass lesions in lobes of the thyroid	R	19p13.2-p12

DTT=defective transport type; F=facilitated transporter; C=cotransporter; E=exchanger; IM=inheritance mode; R=autosomal recessive; D=autosomal dominant.

caused by a *GLUT2* defect is the Fanconi–Bickel syndrome (OMIM 227810 in Table 1) which is inherited in an autosomal recessive mode. It is mainly characterized by hepatorenal glycogen accumulation, proximal renal tubular dysfunction and impaired utilization of glucose and galactose (Manz et al 1987). At least 30 mutations in the *SLC2A2* gene have been reported to be causes of this disease. An interesting example is presented by a deletion mutation generating a premature TGA stop codon at position 74 (g.446–449delT, p.Met74X) (Santer et al 1997). It was found to encode one of the shortest truncated GLUT2 proteins. Some nonsense mutations, substitutions or splice acceptor sites were also found in different patients affected with this disease (Akagi et al 2000; Sakamoto et al 2000; Sanjad et al 1993; Santer et al 1997, 2002).

Another facilitated glucose transporter known to be linked to a human inherited disease is GLUT10, encoded by the *SLC2A10* gene. This gene was cloned from a human liver cDNA library (McVie-Wylie et al 2001). GLUT10 is expressed in many human tissues and organs such as heart, lung, brain, liver, skeletal muscle, pancreas, placenta, kidney and adipose tissue (McVie-Wylie et al 2001; Wood et al 2003). *GLUT10* was first suggested to be a candidate susceptibility gene for non-insulin-dependent diabetes mellitus (McVie-Wylie et al 2001). However, Coucke et al reported the mapping of the arterial tortuosity syndrome (ATS) to the 20q13 locus where *SLC2A10* is located (Coucke et al 2003). ATS is a rare autosomal recessive connective-tissue disorder, characterized by widespread arterial involvement with elongation, tortuosity, stenosis and aneurysms of the large and middle-sized arteries (OMIM 208050 in Table 1). The pathogenesis of ATS seems to be due to the upregulation of the TGFβ signalling pathway (Coucke et al 2006). However, the mechanisms by which mutations in the *SLC2A10* gene lead to TGFβ activation are still unknown.

Inborn errors of the *SLC5* gene family

The second family of mammalian glucose transporters is the 'SLC5 Na^+/glucose cotransporter family'. The first reported member of this family is the Na^+/glucose cotransporter 1 (SGLT1) encoded by the *SLC5A1* gene. It was identified by expression cloning with *Xenopus* oocytes (Hediger et al 1987). There are 11 gene members in this SLC5 family. Most of them function as Na^+-coupled substrate transporters. Transported substrates include glucose, *myo*-inositol, mannose,

vitamins, monocarboxylates and iodide (Agus et al 1997; Kanai et al 1994; Roll et al 2002; Smanik et al 1997; Srinivas et al 2005; Tazawa et al 2005). SGLT1 mediates secondary active glucose absorption across brush border membrane of epithelial cells in the intestine. This function explains the phenotype of the inherited disease linked to *SGLT1* defects, called glucose/galactose malabsorption (GGM), which is characterized by diarrhoea and dehydration (see OMIM 606824 in Table 1). Around 50 mutations were found in patients with GGM (Lam et al 1999; Martin et al 1996; Turk et al 1991, 1994). The first mutation was demonstrated in two sisters with glucose/galactose malabsorption. It was a G>A transition at nucleotide 92, resulting in an aspartate-to-asparagine substitution at position 28 in the transporter protein (g.92 G>A, p.Asp28Asn) (Turk et al 1991). Although missense mutations can lead to the synthesis of full-length proteins, these involved in GGM cause defects in trafficking of the proteins to the plasma membrane (Turk et al 1993). Another group showed that in 15 patients with missense mutations, the function of SLC5A1 was directly impaired (Martin et al 1996). Nonsense or frameshift mutations result in truncated proteins that are not functional.

The human SLC5A2 (alias SGLT2) was demonstrated to be a kidney-specific transporter. It functions as a low-affinity high-capacity Na^+-glucose cotransporter (Kanai et al 1994). Detailed localization studies demonstrated that SGLT2 is expressed in the apical membranes of S1 and also S2 segments of the proximal tubule (PT) cells. SGLT2 is responsible for reabsorption of the bulk of filtered D-glucose. It does not transport D-galactose. In contrast, intestinal SGLT1 is a high-affinity low-capacity glucose and galactose transporter. In the kidney, SGLT1 is expressed in proximal tubule S3 segments where it reabsorbs any residual glucose which escaped the S1 and S2 segments. Not too surprisingly, it was proposed that a defect in the *SGLT2* gene could be involved in the familial form of renal glucosuria (RG; OMIM 233100 in Table 1). The clinical symptoms of this autosomal recessive disorder are substantial daily loss of glucose, despite a normal glucose tolerance test. To date, about 26 mutations have been described in patients with RG. In 2002, homozygosity for a nonsense mutation was demonstrated in a patient with RG (van den Heuvel et al 2002). Moreover, other truncating mutations were found in the *SLC5A2* gene in patients with RG (Calado et al 2004). Extensive analysis of RG patients by Santer and collaborators confirmed the important role of the SCL5A2 glucose transporter in renal tubular glucose reabsorption (Santer et al 2003).

The human sodium/iodide symporter (NIS) which also transports other monovalent anions, is encoded by the fifth member of the SLC5 transporter group (Smanik et al 1996). The primary function of this transporter is to take up I^- from blood across the basolateral membrane of the thyroid follicular cells in order to secrete I^- through the SLC26A4 anion exchanger into the follicular lumen, wherein organification of I^- occurs that is necessary for the synthesis of the T_3 and T_4 thyroid hormones. The NIS transporter is also expressed in colon, breast and ovary (Smanik et al 1996, 1997). Studies on the regulation of the *NIS* gene revealed that the *NIS* gene expression is tightly controlled by the thyroid-stimulating hormone and the thyroid transcription factor and that DNA methylation plays a role in loss of *SLC5A5* gene expression in thyroid carcinomas (Ohmori et al 1998; Venkataraman et al 1999). *SLC5A5* gene expression appears to play a key role in thyroid gland function. As expected, the first mutation in the *NIS* gene was found in a patient with an iodide transport defect in the synthesis of thyroid hormones (OMIM 274400 in Table 1). This defect is characterized by an inability of the thyroid to maintain a concentration difference of iodide between the plasma and the thyroid gland. Symptoms of this patient were mild goitre and multiple mass lesions in lobes of the thyroid. The mutation identified was a single A>C transversion which replaced threonine by proline at position 354 (c.1060A>C, p.Thr354Pro) (Fujiwara 1997). To date, eight different mutations were found in patients with thyroid hormogenesis defects, including 5 missense mutations, 2 nonsense mutations and 1 deletion mutation (Kosugi et al 1998, 1999, 2002; Pohlenz et al 1998). These mutations are believed to decrease the SLC5A5 transport activity at the plasma membrane.

Amino acid transport

Amino acids are required for protein synthesis and they also represent an important source of nitrogen. Some amino acids are considered essential, because cells cannot synthesize them. The liver is the major site of nitrogen metabolism in the body. Amino acids can be divided into three families: those that are glucogenic, those that are ketogenic or those that are both. Amino acids are precursors of the formation of glucose or acetyl-CoA and these two products are essential for ATP production by the Krebs cycle. Another very important role for amino acids is their function as neurotransmitters such as glutamate, aspartate and γ-aminobutyrate. The amino acids

glutamate and aspartate are excitatory neurotransmitters which are released at glutamatergic synapses of the mammalian central nervous system. An accumulation of extracellular excitatory amino acids can be excitotoxic.

The following SLC gene families are associated with amino acid transporter disorders: the *SLC1* family encoding glutamate and neutral amino acid transporters, the *SLC3* family encoding the heavy subunits of heteromeric amino acid transporters, the *SLC6* family encoding Na^+- and Cl^--dependent neurotransmitter transporters, the *SLC7* family encoding the cationic amino acid/glycoprotein-associated amino acid transporters, and the *SLC25* family encoding mitochondrial transporters.

Inborn errors of the *SLC1* gene family

The SLC1 family consists of seven transporters. Several of these transporters are expressed both in epithelial tissues and in neurons or glial cells of the central nervous system: five high-affinity glutamate transporters and two neutral amino acid transporters. The glutamate transporters mediate the transport of L-Glu, L-Asp and D-Asp, accompanied by the co-transport of Na^+ and H^+ and the countertransport of K^+. The membrane topology model of these transporters shows special features in that the central domain possesses 8 transmembrane (TM) segments and 3 re-entrant loops, with both amino- and carboxyl-termini in the cytosol (Grunewald and Kanner 2000; Torres and Amara 2007). Because of the importance of these transporters in neurotransmission, genetic diseases associated with their dysfunction are expected to be rare. Nevertheless, a heterozygous mutation (g.1047C>G, p.Pro290Arg) in the *SLC1A3* gene (alias *excitatory amino acid transporter 1* or *EAAT1*) was found in only a single patient with episodic ataxia, seizures, migraine, and alternating hemiplegia (Jen et al 2005). This mutation was not present in the patient's asymptomatic parents, suggesting that it arose *de novo*. Functional studies showed that the missense substitution leads to decrease of both glutamate uptake and EAAT1 expression to plasma membrane, which contributes to neuronal hyperexcitability in the patient (Jen et al 2005). However, no further information is known about this mutation and its clinical relevance.

Inborn errors of the *SLC3* gene family

The family of *SLC3* genes consists of two genes, *rBAT* and *4F2hc*, encoding proteins with one single transmembrane domain: a large extracellular glycosylated C-terminus and a short intracellular N-terminus (type II membrane glycoproteins). The proteins of the SLC3 family form the so-called heavy subunits of heteromeric amino acid transporters (HATs). In these transporters, the light subunits, which are members of the SLC7 family (described below), form the actual transporter unit (Wagner et al 2001).

By expression cloning using *Xenopus* oocytes, rBAT (related to $b^{0,+}$ amino acid transporter) cDNA was identified, which is named SLC3A1. rBAT is expressed in the apical plasma membrane of epithelial cells in kidney and small intestine where it is involved in transport of cystine and dibasic and neutral amino acids (Palacin and Kanai 2004; Wells et al 1992). Cystinuria is characterized by cystine precipitation inducing the formation of calculi in the urinary tract, which leads to obstruction, infection and finally renal insufficiency (OMIM 220100 in Table 2). Cystinuria is a rare disorder which has an autosomal recessive transmission mode (Calonge et al 1995; Garrod and Hurtley 1906; Palacin et al 2001). In general, the excretion of both cystine and dibasic amino acids is increased in the urine in patients with cystinuria.

Mutations in the *SLC3A1* and *SLC7A9* genes are responsible for the disease. The disease can be divided into phenotype A (normal amino aciduria in heterozygotes) and phenotype B (moderate to high hyperexcretion of cystine and dibasic amino acids in heterozygotes). Cystinuria type A is caused by mutations in the *SLC3A1* gene, whereas mutations in the *SLC7A9* gene cause cystinuria type B, in addition to some cases of cystinuria 'type I' (Calonge et al 1994, 1995; Dello Strologo et al 2002). In 2002, Dello Strologo et al suggested that this classification system should be replaced by a new one: type A due to mutations in the *SLC3A1* gene, type B due to mutations in the *SLC7A9* gene, and type A/B due to mutations in both the *SLC3A1* and *SLC7A9* genes (Dello Strologo et al 2002). To date, more than 60 mutations in the *SLC3A1* gene have been identified, mostly missense mutations (Palacin et al 2001).

Inborn errors of the *SLC7* gene family

The SLC7 family corresponds to the cationic amino acid transporters (CAT). They also include the glycoprotein-associated amino acid transporters (gpaAT). The *SLC7* family contains 11 genes. This family can be further divided into two functional subgroups, the CAT group (SLC7A1–4) and the gpaAT group (SLC7A5–11), also called light chains of the heterodimeric amino acid transporters HAT (see above)

Table 2 Inborn errors of amino acid metabolism caused by faulty cell surface SLCs

SLC member, DTT: substrates	OMIM no.	Disease name	Clinical, molecular and biological features	IM	Locus
SLC1A3, M: Na^+, H^+, glutamate/K^+	600111	Episodic ataxia, type 6	Episodic ataxia, seizure, migraine, alternating hemiplegia	–	5p13
SLC3A1, E: cystine/dibasic amino acid	220100	Cystinuria, type A	Increased excretion of cystine and dibasic amino acids; formation of cystine calculi	R	2p16.3
SLC6A19, C: Na^+/neutral amino acid	234500	Hartnup disorder	Pellagra-like light-sensitive rash, cerebellar ataxia, emotional instability, and aminoaciduria	R	5p15
SLC7A7, E: cationic/neutral amino acid	222700	Lysinuric protein intolerance	Severe mental retardation, physical retardation, mild intestinal malabsorption syndrome, increased urinary excretion of lysine, ornithine and arginine	R	14q11.2
SLC7A9, E: cystine/dibasic amino acid	220100	Cystinuria, type B	Cystine precipitation, formation of calculi in the urinary tract, renal insufficiency	R	19q13.1
SLC25A22 M: glutamate/H^+or OH^-	609304	Neonatal myoclonic epilepsy with suppression-burst pattern	Intractable epileptic syndromes with either neonatal onset or onset during the first months of life, and neonatal hypotonia. Characterized by a typical electroencephalogram pattern—namely, suppression burst, in which higher-voltage bursts of slow waves mixed with multifocal spikes alternate with isoelectric suppression phases. Brain atrophy and abnormal visual nerve-conduction velocity have been also observed.	R	11p15.5

DTT=defective transport type; M=multiporter; C=cotransporter; E=exchanger; IM=inheritance mode; R=autosomal recessive; D=autosomal dominant.

(Deves et al 1998; Kim et al 1991). In general, CATs function as facilitated transporters, whereas gpaATs mostly function as obligatory exchangers. They also largely differ in their predicted structure, in that the CATs have 14 putative TM segments and are glycosylated, whereas the gpaATs have 12 TM domains, are not glycosylated and need to associate with a glycoprotein of the SLC3 superfamily (4F2hc or rBAT) for surface expression.

Two *gpaAT* genes were identified as linked to human inherited disease. The first is *SLC7A7* and encodes the y^+L-type amino acid transporter 1 (y^+LAT1) which has been shown to mediate preferentially the exchange of cytosolic cationic amino acid for extracellular neutral amino acid (Torrents et al 1998). The causal gene in lysinuric protein intolerance (LPI; see OMIM 222700 in Table 2) was mapped to the locus 14q11.2 corresponding to the same chromosomal region as the *SLC7A7* gene. These results strongly suggest that dysfunction of y^+LAT1 is a cause of LPI. Indeed, a defect in the plasma membrane transport of dibasic amino acids was demonstrated at the basolateral membrane of renal tubule epithelial cells, in small intestine and in skin fibroblasts from patients with LPI. LPI is a rare autosomal recessive disease and symptoms of LPI were described as severe mental retardation, physical retardation, mild intestinal malabsorption syndrome and increase in urinary excretion of lysine, ornithine and arginine (Oyanagi et al 1970). Mutated SLC7A7 proteins were initially found in 31 Finnish patients and 1 Spanish patient with LPI. The Finnish patients were homozygous for a missense mutation leading to a premature stop codon (g.1181A>T, p.Phe308X). This mutation abolishes an acceptor AG splice site at the end of the intron and leads to cryptic splicing at the next AG site, 10 bp downstream. The Spanish patient was a compound heterozygote with a frameshift mutation (g.1291delCTTT) in one allele and a missense mutation (g.1287T>G, p.Lys334Arg) on the other allele (Torrents et al 1999). To date, about 20 mutations were found in the *SLC7A7* gene of patients with LPI.

The other *SLC7* gene linked to an inherited disease is *SLC7A9* encoding the $b^{0,+}$ amino acid transporter. This transporter was found to be expressed in kidney, liver, small intestine and placenta where, in contrast to SLC7A7, it mediates preferentially the exchange of extracellular cationic amino acids for intracellular neutral amino acids (Feliubadalo et al 1999). As noted above, mutations in this gene were shown to be linked to cystinuria type B. Numerous mutations in the *SLC7A9* gene were found in patients with cystinuria (Font et al 2001).

Inborn errors of the *SLC6* gene family

Transporters of the *SLC6* gene family belong to the sodium- and chloride-dependent neurotransmitter transporter family which includes 20 members. These genes encode proteins having probably 12 transmembrane domains. Among family members are transporters of neurotransmitters, osmolytes and creatine. Other members correspond to the previously described classical Na^+-dependent amino acid uptake systems.

Several members of the *SLC6* family are linked to inherited diseases. Many are associated with primarily neurological disorders and are therefore not discussed further in this overview. Defects of *SLC6A19* are related to a type of amino aciduria. This gene encodes the system B^0 transporter, called B^0 AT1. High levels of expression of SLC6A19 were found in the apical membrane of renal and small intestinal epithelial cells. Functional studies in *Xenopus* oocytes showed that the SLC6A19-mediated transport is electrogenic and Na^+- and pH-dependent, and that, in contrast to other analogues of the SLC6 superfamily, it is Cl^--independent (Broer et al 2004; Kleta et al 2004). Using homozygosity mapping, Kleta and collaborators confirmed that the causative gene in the Hartnup disorder is located on locus 5p15 and corresponds to *SLC6A19* (Kleta et al 2004). This disorder is an autosomal recessive disorder which is characterized by a pellagra-like light-sensitive rash, cerebellar ataxia, emotional instability, and amino aciduria (OMIM 234500 in Table 2). Ten different mutations have been described to date causing this disease. One mutation, the p.Asp173Asn allele, is present in 42% of Hartnup chromosomes from unrelated families from Australia and North America (Azmanov et al 2007). These mutations apparently reduce the transport function of neutral amino acids across epithelial cells in renal proximal tubules and intestinal mucosa.

Iminoglycinuria is a rare autosomal recessive disorder characterized by increased urinary excretion of proline, hydroxyproline and glycine, resulting in neurosensory hearing loss and ichthyosis, which may be associated with mental retardation (Goyer et al 1968; Swarna et al 2004). Iminoglycinuria has been suggested to be caused by defects of renal tubule amino acid transporters. The gene product of *SLC6A20* (also known as *sodium imino acid transporter 1* or *SIT1*) has been characterized recently (Takanaga et al 2005). Its functional properties were shown to correspond to those of the classical system IMINO which mediates Na^+-dependent proline uptake into epithelial cells of kidney and intestine. It is tempting to speculate that mutations in the *SLC6A20* gene are the cause of some cases of hereditary iminoaciduria. However, the precise genetic defects of this disease have not yet been elucidated.

Inborn errors of the *SLC25* gene family

Members of the SLC25 family of mitochondrial carriers also transport amino acids, and defects of their genes can be involved in such human pathologies as seizures. One example has been described recently and concerns defects of the *SLC25A22* gene, which encodes a ubiquitous glutamate multiporter (transport of l-glutamate either with H^+ or in exchange for OH^-; see Fig. 1) (Fiermonte et al 2002). Molinari and colleagues found the *SLC25A22* gene within the interval on 11p15.5 linked to neonatal myoclonic epilepsy with suppression-burst pattern (OMIM 609304 in Table 2). This inherited disease has an autosomal recessive transmission mode and is principally characterized by early-onset severe seizures and neonatal hypotonia. In the same work, Molinari and colleagues reported the identification of a homozygous missense mutation in the *SLC25A22* gene (p.Pro206Leu) which causes impaired mitochondrial glutamate transport and consequently seizures in the affected children (Molinari et al 2005).

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References

Agus DB, Gambhir SS, Pardridge WM, et al (1997) Vitamin C crosses the blood–brain barrier in the oxidized form through the glucose transporters. *J Clin Invest* **100**: 2842–2848.

Akagi M, Inui K, Nakajima S, et al (2000) Mutation analysis of two Japanese patients with Fanconi-Bickel syndrome. *J Hum Genet* **45**: 60–62.

Azmanov DN, Rodgers H, Auray-Blais C, et al (2007) Persistence of the common Hartnup disease d173(n)under-bar allele in populations of European origin. *Ann Hum Genet* **71**: 755–761.

Brockmann K, Wang D, Korenke CG, et al (2001) Autosomal dominant GLUT-1 deficiency syndrome and familial epilepsy. *Ann Neurol* **50**: 476–485.

Broer A, Klingel K, Kowalczuk S, Rasko JEJ, Cavanaugh J, Broer S (2004) Molecular cloning of mouse amino acid transport system B-0, a neutral amino acid transporter related to Hartnup disorder. *J Biol Chem* **279**: 24467–24476.

Calado J, Soto K, Clemente C, Correia P, Rueff J (2004) Novel compound heterozygous mutations in SLC5a2 are responsible for autosomal recessive renal glucosuria. *Hum Genet* **114**: 314–316.

Calonge MT, Gasparini P, Chillaron J, et al (1994) Cystinuria caused by mutations in rBAT, a gene involved in the transport of cystine. *Nat Genet* **6**: 420–425.

Calonge MJ, Volpini V, Bisceglia L, et al (1995) Genetic-heterogeneity in cystinuria—the SLC3a1 gene is linked to type-I but not to type-III cystinuria. *Proc Natl Acad Sci U S A* **92**: 9667–9671.

Coucke PJ, Wessels MW, Van Acker P, et al (2003) Homozygosity mapping of a gene for arterial tortuosity syndrome to chromosome 20q13. *J Med Genet* **40**: 747–751.

Coucke PJ, Willaert A, Wessels MW, et al (2006) Mutations in the facilitative glucose transporter GLUT10 alter angiogenesis and cause arterial tortuosity syndrome. *Nat Genet* **38**: 452–457.

Dello Strologo L, Pras E, Pontesilli C, et al (2002) Comparison between SLC3a1 and SLC7a9 cystinuria patients and carriers: a need for a new classification. *J Am Soc Nephrol* **13**: 2547–2553.

Deves R, Angelo S, Rojas AM (1998) System y(+)l: the broad scope and cation modulated amino acid transporter. *Exp Physiol* **83**: 211–220.

DeVivo DC, Trifiletti RR, Jacobson RI, Ronen GM, Behmand RA, Harik SI (1991) Defective glucose-transport across the blood–brain-barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. *N Engl J Med* **325**: 703–709.

Feliubadalo L, Font M, Purroy J, et al (1999) Non-type I cystinuria caused by mutations in SLC7a9, encoding a subunit (b(o,+)at) of rBAT. *Nat Genet* **23**: 52–57.

Fiermonte G, Palmieri L, Todisco S, Agrimi G, Palmieri F, Walker JE (2002) Identification of the mitochondrial glutamate transporter. Bacterial expression, reconstitution, functional characterization, and tissue distribution of two human isoforms. *J Biol Chem* **277**: 19289–19294.

Font M, Feliubadalo L, Estivill X, et al (2001) Functional analysis of mutations in SLC7a9, and genotype–phenotype correlation in non-type I cystinuria. *Hum Mol Genet* **10**: 305–316.

Fujiwara H (1997) Congenital hypothyroidism caused by a mutation in the Na^+/I- symporter. *Nat Genet* **17**: 122–122.

Fukumoto H, Seino S, Imura H, Seino Y, Bell GI (1988) Characterization and expression of human HEPG2 erythrocyte glucose-transporter gene. *Diabetes* **37**: 657–661.

Gamba G (2005) Molecular physiology and pathophysiology of electroneutral cation-chloride cotransporters. *Physiol Rev* **85**: 423–493.

Garrod E, Hurtley WH (1906) Concerning cystinuria. *J Physiol* **34**: 217–223.

Goyer RA, Reynolds J, Burke J, Burkholder P (1968) Hereditary renal disease with neurosensory hearing loss prolinuria and ichthyosis. *Am J Med Sci* **256**: 166–179.

Grunewald M, Kanner BI (2000) The accessibility of a novel reentrant loop of the glutamate transporter GLT-1 is restricted by its substrate. *J Biol Chem* **275**: 9684–9689.

Hediger MA, Coady MJ, Ikeda TS, Wright EM (1987) Expression cloning and cDNA sequencing of the Na+/glucose co-transporter. *Nature* **330**: 379–381.

Hediger MA, Romero MF, Peng JB, Rolfs A, Takanaga H, Bruford EA (2004) The ABCs of solute carriers: Physiological, pathological and therapeutic implications of human membrane transport proteins—introduction. *Pflugers Arch* **447**: 465–468.

Heilig C, Brosius F, Siu B, et al (2003) Implications of glucose transporter protein type 1 (GLUT1)-hapiodeficiency in embryonic stem cells for their survival in response to hypoxic stress. *Am J Pathol* **163**: 1873–1885.

Ikeda Y, Dick KA, Weatherspoon MR, et al (2006) Spectrin mutations cause spinocerebellar ataxia type 5. *Nat Genet* **38**: 184–190.

Jen JC, Wan J, Palos TP, Howard BD, Baloh RW (2005) Mutation in the glutamate transporter EAAT1 causes episodic ataxia, hemiplegia, and seizures. *Neurology* **65**: 529–534.

Kanai Y, Lee WS, You GF, Brown D, Hediger MA (1994) The human kidney low-affinity Na^+/glucose cotransporter SGLT2—delineation of the major renal reabsorptive mechanism for d-glucose. *J Clin Invest* **93**: 397–404.

Kim JW, Closs EI, Albritton LM, Cunningham JM (1991) Transport of cationic amino-acids by the mouse ecotropic retrovirus receptor. *Nature* **352**: 725–728.

Klepper J, Monden I, Guertsen E, Voit T, Willemsen M, Keller K (2001) Functional consequences of the autosomal dominant G272A mutation in the human GLUT1 gene. *FEBS Lett* **498**: 104–109.

Kleta R, Romeo E, Ristic Z, et al (2004) Mutations in SLC6a19, encoding B(0)AT1, cause Hartnup disorder. *Nat Genet* **36**: 999–1002.

Kosugi S, Inoue S, Matsuda A, Jhiang S (1998) Novel, missense and loss-of-function mutations in the sodium/iodide symporter gene causing iodide transport defect in three Japanese patients. *J Clin Endocrinol Metab* **83**: 3373–3376.

Kosugi S, Bhayana S, Dean HJ (1999) A novel mutation in the sodium/iodide symporter gene in the largest family with iodide transport defect. *J Clin Endocrinol Metab* **84**: 3248–3253.

Kosugi S, Okamoto H, Tamada A, Sanchez-Franco F (2002) A novel peculiar mutation in the sodium/iodide symporter gene in Spanish siblings with iodide transport defect. *J Clin Endocrinol Metab* **87**: 3830–3836.

Lam JT, Martin MG, Turk E, et al (1999) Missense mutations in SGLT1 cause glucose-galactose malabsorption by trafficking defects. *Biochim Biophys Acta* **1453**: 297–303.

Landowski CP, Suzuki Y, Hediger MA. (2005) The mammalian transporter families. In Alpern RJ, Henert SC, eds. *Seldin and Giebisch's The Kidney. Physiology and Pathophysiology*, 2 vols, 4th edn. New Haven: Elsevier, 91–146.

Manz F, Bickel H, Brodehl J, et al (1987) Fanconi–Bickel syndrome. *Pediatr Nephrol* **1**: 509–518.

Martin MG, Turk E, Lostao MP, Kerner C, Wright EM (1996) Defects in Na^+ glucose cotransporter (SGLT1) trafficking and function cause glucose-galactose malabsorption. *Nat Genet* **12**: 216–220.

McVie-Wylie AJ, Lamson DR, Chen YT (2001) Molecular cloning of a novel member of the GLUT family of transporters, SLC2a10 (GLUT10), localized on chromosome 20q13.1: a candidate gene for NIDDM susceptibility. *Genomics* **72**: 113–117.

Molinari F, Raas-Rothschild A, Rio M, et al (2005) Impaired mitochondrial glutamate transport in autosomal recessive neonatal myoclonic epilepsy. *Am J Hum Genet* **76**: 334–339.

Mueckler M, Caruso C, Baldwin SA, et al (1985) Sequence and structure of a human glucose transporter. *Science* **229**: 941–945.

Mueckler M, Kruse M, Strube M, Riggs AC, Chiu KC, Permutt MA (1994) A mutation in the GLUT2 glucose-transporter gene of a diabetic patient abolishes transport activity. *J Biol Chem* **269**: 17765–17767.

Ohmori M, Endo T, Harii N, Onaya T (1998) A novel thyroid transcription factor is essential for thyrotropin-induced up-regulation of Na^+/I- symporter gene expression. *Mol Endocrinol* **12**: 727–736.

Orci L, Thorens B, Ravazzola M, Lodish HF (1989) Localization of the pancreatic beta-cell glucose transporter to specific plasma-membrane domains. *Science* **245**: 295–297.

Oyanagi K, Miura R, Yamanouc T (1970) Congenital lysinuria—a new inherited transport disorder of dibasic amino acids. *J Pediatr* **77**: 259–266.

Palacin M, Kanai Y (2004) The ancillary proteins of hats: SLC3 family of amino acid transporters. *Pflugers Arch* **447**: 490–494.

Palacin M, Fernandez E, Chillaron J, Zorzano A (2001) The amino acid transport system b(o,+) and cystinuria. *Mol Membr Biol* **18**: 21–26.

Pohlenz J, Rosenthal IM, Weiss RE, Jhiang SM, Burant C, Refetoff S (1998) Congenital hypothyroidism due to mutations in the sodium/iodide symporter. Identification of a nonsense mutation producing a downstream cryptic 3′ splice site. *J Clin Invest* **101**: 1028–1035.

Roll P, Massacrier A, Pereira S, Robaglia-Schlupp A, Cau P, Szepetowski P (2002) New human sodium/glucose cotransporter gene (KST1): identification, characterization, and mutation analysis in ICCA (infantile convulsions and choreoathetosis) and BFIC (benign familial infantile convulsions) families. *Gene* **285**: 141–148.

Sakamoto O, Ogawa E, Ohura T, et al (2000) Mutation analysis of the GLUT2 gene in patients with Fanconi-Bickel syndrome. *Pediatr Res* **48**: 586–589.

Sanjad SA, Kaddoura RE, Nazer HM, Akhtar M, Sakati NA (1993) Fanconis-syndrome with hepatorenal glycogenosis associated with phosphorylase-b kinase-deficiency. *Am J Dis Child* **147**: 957–959.

Santer R, Schneppenheim R, Dombrowski A, Gotze H, Steinmann B, Schaub J (1997) Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with Fanconi–Bickel syndrome. *Nat Genet* **17**: 324–326.

Santer R, Groth S, Kinner M, et al (2002) The mutation spectrum of the facilitative glucose transporter gene SLC2a2 (GLUT2) in patients with Fanconi–Bickel syndrome. *Hum Genet* **110**: 21–29.

Santer R, Kinner M, Lassen CL, et al (2003) Molecular analysis of the SGLT2 gene in patients with renal glucosuria. *J Am Soc Nephrol* **14**: 2873–2882.

Seidner G, Alvarez MG, Yeh JI, et al (1998) GLUT-1 deficiency syndrome caused by haploinsufficiency of the blood–brain barrier hexose carrier. *Nat Genet* **18**: 188–191.

Smanik PA, Liu Q, Furminger TL, et al (1996) Cloning of the human sodium iodide symporter. *Biochem Biophys Res Commun* **226**: 339–345.

Smanik PA, Ryu KY, Theil KS, Mazzaferri EL, Jhiang SM (1997) Expression, exon-intron organization, and chromosome mapping of the human sodium iodide symporter. *Endocrinology* **138**: 3555–3558.

Srinivas SR, Gopal E, Zhuang L, et al (2005) Cloning and functional identification of SLC5a12 as a sodium-coupled low-affinity transporter for monocarboxylates (SMCT2). *Biochem J* **392**: 655–664.

Swarna M, Jyothy A, Rani PU, Reddy PP (2004) Amino acid disorders in mental retardation: A two-decade study from Andhra Pradesh. *Biochem Genet* **42**: 85–98.

Takanaga H, Mackenzie B, Suzuki Y, Hediger MA (2005) Identification of mammalian proline transporter SIT1 (SLC6a20) with characteristics of classical system imino. *J Biol Chem* **280**: 8974–8984.

Tanizawa Y, Riggs AC, Chiu KC, et al (1994) Variability of the pancreatic-islet beta-cell liver (GLUT-2) glucose-transporter gene in NIDDM patients. *Diabetologia* **37**: 420–427.

Tazawa S, Yamato T, Fujikura H, et al (2005) SLC5a9/SGLT4, a new Na^+-dependent glucose transporter, is an essential transporter for mannose, 1,5-anhydro-d-glucitol, and fructose. *Life Sci* **76**: 1039–1050.

Torrents D, Estevez R, Pineda M, et al (1998) Identification and characterization of a membrane protein (y(+)l amino acid transporter-1) that associates with 4F2hc to encode the amino acid transport activity y(+)l—a candidate gene for lysinuric protein intolerance. *J Biol Chem* **273**: 32437–32445.

Torrents D, Mykkanen J, Pineda M, et al (1999) Identification of SLC7a7, encoding y(+)LAt-1, as the lysinuric protein intolerance gene. *Nat Genet* **21**: 293–296.

Torres GE, Amara SG (2007) Glutamate and monoamine transporters: new visions of form and function. *Curr Opin Neurobiol* **17**: 304–312.

Turk E, Zabel B, Mundlos S, Dyer J, Wright EM (1991) Glucose galactose malabsorption caused by a defect in the Na^+/glucose cotransporter. *Nature* **350**: 354–356.

Turk E, Klisak I, Bacallao R, Sparkes RS, Wright EM (1993) Assignment of the human Na^+/glucose cotransporter gene-SGLT1 to chromosome-22q13.1. *Genomics* **17**: 752–754.

Turk E, Martin MG, Wright EM (1994) Structure of the human Na^+/glucose cotransporter gene SGLT1. *J Biol Chem* **269**: 15204–15209.

van den Heuvel L, Assink K, Willemsen M, Monnens L (2002) Autosomal recessive renal glucosuria attributable to a mutation in the sodium glucose cotransporter (SGLT2). *Hum Genet* **111**: 544–547.

Venkataraman GM, Yatin M, Marcinek R, Ain KB (1999) Restoration of iodide uptake in dedifferentiated thyroid carcinoma: Relationship to human Na^+/I- symporter gene methylation status. *J Clin Endocrinol Metab* **84**: 2449–2457.

Wagner CA, Lang F, Broer S (2001) Function and structure of heterodimeric amino acid transporters. *Am J Physiol Cell Physiol* **281**: C1077–C1093.

Wang D, Kranz-Eble P, DeVivo DC (2000) Mutational analysis of GLUT1 (SLC2a1) in GLUT-1 deficiency syndrome. *Hum Mutat* **16**: 527–527.

Wells RG, Pajor AM, Kanai Y, Turk E, Wright EM, Hediger MA (1992) Cloning of a human kidney cDNA with similarity to the sodium-glucose cotransporter. *Am J Physiol* **263**: F459–F465.

Wood IS, Hunter L, Trayhurn P (2003) Expression of class III facilitative glucose transporter genes (GLUT-10 and GLUT-12) in mouse and human adipose tissues. *Biochem Biophys Res Commun* **308**: 43–49.